Structure of the GAF Domain, a Ubiquitous Signaling Motif and a new Class of Cyclic GMP Receptor

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GAF domains are ubiquitous motifs present in cyclic **G**MP-regulated cyclic nucleotide phosphodiesterases, certain **a**denylyl cyclases, the bacterial transcription factor **F**hlA, and hundreds of other signaling and sensory proteins from all three kingdoms of life. The crystal structure of the Saccharomyces cerevisiae YKG9 protein was determined at 1.9 Å resolution. The structure revealed a fold that resembles the PAS domain, another ubiquitous signaling and sensory transducer. YKG9 does not bind cyclic GMP, but the isolated first GAF domain of phosphodiesterase 5 binds with K_d = 650 nM. The cyclic GMP binding site of the phosphodiesterase GAF domain was identified by homology modeling and site-directed mutagenesis, and consists of conserved Arg, Asn, Lys, and Asp residues. The structural and binding studies taken together show that the cyclic GMP-binding GAF domains form a new class of cyclic nucleotide receptors distinct from the regulatory domains of cyclic nucleotide-regulated protein kinases and ion channels.